Remarks

Co-Pending Application

Applicants bring co-pending application U.S. Ser. No. 10/070,416, which is before Examiner Maier, to the Examiner's attention. This co-pending application may contain technology similar to the instant invention.

The Amendments

Claims 7, 12, 17, and 21-24 have been canceled without prejudice to their prosecution in a continuing application. Claims 2, 3, 4, 5, 6, 8, 9, 13, and 15 have been amended to change the term "A" to "The". This is not a narrowing amendment. Claims 10, 11, 18, 19, and 20 have been amended to clarify that the claims are method claims. Support for the amendments can be found in the specification at, *inter alia*, page 2, line 35 through page 3, line14; page 5, line 10 through page 6, line 15. This is not a narrowing amendment. New claims 25-27 have been added. New claim 25 finds support in the specification at, *inter alia*, page 6, lines 16-25. New claims 26 and 27 find support in the specification at, *inter alia*, page 4, lines 6-9.

Objection to Claims 2-22

The Office Action has objected to claims 2-22. The Office Action has requested that the term "A" before the term "formulation" or "product" should be changed to "The". The amendments have been made. Applicants request withdrawal of the objection.

Rejection of Claims 7, 10, 11, and 17-22 Under 35 U.S.C. §112, second paragraph

Claims 7, 10, 11, and 17-22 stand rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite. Claims 7, 17, 21, and 22 have been canceled. As such,

the rejection is moot as applied to claims 7, 17, 21 and 22. Applicants respectfully traverse the rejection as it applies to claims 10, 11, and 18-20.

The Office Action asserts that claims 10, 11, 18-20 do not confer patentable distinction on previous claims. Claims 10, 11, 18-20 have been amended to clarify that the claims are method claims.

Claims 21 and 22 have been canceled.

The Office Action asserts that the term 950 mg/m^2 is unclear as a dosage unit. However, mg/m^2 is a well-recognized dosage unit. mg/m^2 stands for Body Surface Area (see e.g., Cancer Chemotherapy Reports 50(4):219 (1966)). Applicants have attached a small sample of the multitude of abstracts listed in PubMed (National Library of Medicine) that report calculating dosage using Body Surface Area (mg/m^2). One of skill in the art would understand that the mg/m^2 dosage refers to Body Surface Area. As such, the claim is definite and Applicants respectfully request withdrawal of the rejection.

Rejection of Claims 23 and 24 Under 35 U.S.C. §101

Claims 23 and 24 stand rejected under 35 U.S.C. §101 as improper process claims. Claims 23 and 24 have been canceled. Applicant respectfully request withdrawal of the rejection.

Rejection of Claims 1-22 Under 35 U.S.C. §103(a)

Claims 1-22 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Martini et al. (WO 96/09072) in combination with Stella et al. (U.S. Pat. No. 5,134,127) in view of Yoshida et al. (WO 84/02270).

The Office Action asserts that Martini teaches a composition comprising an estramustine phosphate and a cyclodextrin, Stella teaches a method of using sulfoalkyl cyclodextrin derivatives as solubilizing agents for water insoluble drugs, and Yoshida disclose the use of estramustine phosphate in microfine particles where albumin can be converted to microfine particles as carriers. The Office Action furthermore asserts that one of skill in the art would have a reasonable expectation of success in combining the teachings of these references to accomplish the formulations and methods of the invention. The Office asserts that Martini provides the motivation for doing so because Martini discloses a pharmaceutical composition containing an estramustine derivative and a cyclodextrin, which is suitable for oral administration to a cancer patient.

Initially, Martini teaches the combination of estramustine derivatives with certain cyclodextrins for use in oral formulations. Martini teaches that estramustine-17-phosphate has strong limitations when orally administrated. See paragraph spanning page 3 and 4. Although water soluble, *per se*, estramustine derivatives can precipitate in the gastrointestinal tract due to contact with cations present in the gastrointestinal tract. See page 3, line 23 through page 4, line 5. Martini combines estramustine derivatives with certain cyclodextrins to address the limitations of oral administration of estramustine. See page 5, last paragraph. Martini does not teach or suggest parenteral formulations of estramustine phosphate, which are claimed in the instant application.

Secondly, Stella teaches that sulfoalkyl ether cyclodextrins derivatives are useful as solubilizing agents for water insoluble drugs. See abstract; Col. 2, lines 3-4 Estramustine phosphate is water soluble. See e.g., Emcyt® product sheet, "Clinical Pharmacology" section (copy attached). As such, one of skill in the art would not seek to

use a solubilization agent for parenteral administration of water soluble estramustine phosphate.

Applicants submit that the Office Action has not established a *prima facia* case of obviousness. To establish a *prima facia* case of obviousness there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See MPEP §2143.

There is no suggestion nor motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. There must be some reason, suggestion, or motivation found in the cited references whereby a person of ordinary skill in the field of the invention would make the substitutions required. That knowledge cannot come from the applicants' disclosure of the invention itself. *Diversitech Corp. v. Century Steps, Inc.*, 7 U.S.P.Q.2d 1315,1318 (Fed. Cir. 1988); *In re Geiger*, 2 U.S.P.Q.2d 1276, 1278 (Fed. Cir. 1987); *Interconnect Planning Corp. v. Feil*, 227 U.S.P.Q. 543, 551 (Fed. Cir. 1985).

None of the cited references, alone or in combination, suggests a parenteral formulation comprising a parenterally acceptable carrier or diluent, estramustine phosphate, a sulfoalkyl ether cyclodextrin, and human albumin. Martini does not teach or suggest the parenteral administration of estramustine phosphate. Stella does not teach or suggest that the disclosed cyclodextrins would be useful for the parenteral administration of water soluble drugs such as estramustine phosphate. Yoshida does not provide the missing motivation. As such, one of skill in the art would not be motivated to combine a reference teaching the oral administration of estramustine phosphate with a reference

teaching solubilizing agents, and a reference teaching the use of estramustine phosphate in microfine particles to solve the problem of parenteral administration of estramustine phosphate.

Despite the fact that a *prima facia* case of obviousness has not been established, the claims are also rendered non-obvious because the claimed methods and formulations provide unexpected, advantageous properties. See MPEP §716.02. The advantageous properties are unexpected and are of practical significance. Parenterally administered estramustine phosphate can cause vascular damage at the site of the injection, including local irritations, ulcerative damage, and thrombophlebitis. See specification, page 1, last paragraph. The formulations of the invention provide the unexpected, advantageous property of reducing the side effects of parenteral administration of estramustine phosphate, including the reduction of local irritation, ulcerative damage, and thrombophlebitis. See specification at page 6, line 25 through page 8, line 25 (comparing the local irritant effects of parenteral administration of (1) water; (2) estramustine phosphate; (3) estramustine phosphate and sulfoalkyl ether cyclodextrin and (4) estramustine phosphate and human albumin; and (5) estramustine phosphate, sulfoalkyl ether cyclodextrin, and human albumin in rats).

Therefore, the claimed methods and formulations are not obvious in view of Martini and Stella in view of Yoshida because (1) there is no motivation or suggestion to combine the cited references; and (2) the claimed methods and formulations provide unexpected, superior therapeutic activity.

Conclusion

In view of the above remarks, the application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issue.

Respectfully submitted,

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